



(12) **United States Patent**  
**Weyand et al.**

(10) **Patent No.:** **US 9,511,086 B2**  
(45) **Date of Patent:** **Dec. 6, 2016**

(54) **METHOD FOR IMPROVING IMMUNE SYSTEM FUNCTION BY ADMINISTERING AGENTS THAT INHIBIT DNA-DEPENDENT PROTEIN KINASE-DIRECTED APOPTOSIS**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/205,001**

(22) Filed: **Aug. 8, 2011**

(65) **Prior Publication Data**

US 2012/0039867 A1 Feb. 16, 2012

**Related U.S. Application Data**

(60) Provisional application No. 61/372,829, filed on Aug. 11, 2010.

(51) **Int. Cl.**

**A61K 31/7088** (2006.01)

**A61K 31/7105** (2006.01)

**A61K 31/711** (2006.01)

**G01N 33/50** (2006.01)

**A61K 38/00** (2006.01)

(52) **U.S. Cl.**

CPC ..... **A61K 31/7088** (2013.01); **A61K 31/711** (2013.01); **A61K 31/7105** (2013.01); **G01N 33/5008** (2013.01); **A61K 38/00** (2013.01); **G01N 2800/102** (2013.01)

(58) **Field of Classification Search**

CPC ..... **A61K 31/7088**; **A61K 31/7105**; **A61K 31/711**; **A61K 31/12**

See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

2007/0003531 A1\* 1/2007 Mukherji et al. .... 424/93.21

**OTHER PUBLICATIONS**

Shao L et al. Deficiency of the DNA repair enzyme ATM in rheumatoid arthritis. J. Exp. Med. 206 (6): 1435-1449, 2009.\*

Christmann et al. Mechanisms of DNA repair: an update. Toxicology 193: 3-34, 2003.\*

Scarpaci et al. DNA damage recognition and repair capacities in human naïve and memory T cells from peripheral blood of young and elderly subjects. Mechanisms of Aging. 124:517-524, 2003.\*

Luo et al. Gene of DNA-dependent protein kinase catalytic subunit in chronic myeloid leukemia. Journal of experimental hematology. 15(2):248-52, 2007—Abstract only.\*

Lin et al. Increased apoptosis of peripheral blood T cells following allogeneic hematopoietic cell transplantation. Blood. 95(12):3832-3839, 2000.\*

Shao et al. Deficiency of the DNA repair enzyme ATM in rheumatoid arthritis. Journal of Experimental Medicine 206(6):1435-1449, 2009.\*

Maurer et al. Evidence for the presence of activated CD4 T cells with a naïve phenotype in the peripheral blood of patients with rheumatoid arthritis. Clinical Experimental Immunology. 87:429-434, 1992.\*

Park et al. Involvement of DNA-dependent kinase in regulation of stress-induced JNK activation. DNA and Cell Biology. 20(10):637-645, 2001.\*

Shrivastav et al. Regulation of DNA double strand break repair pathway choice. Cell Research. 18:134-147, 2008.\*

Maurer et al. Evidence for the presence of activated CD4 T cells with naïve phenotype in the peripheral blood of patients with rheumatoid arthritis. Clinical Experimental Immunology. 1992; 87:429-434.\*

Christmann et al. Mechanisms of human DNA repair: an update. Toxicology. 2003; 193:3-34.\*

Sedelnikova et al. Delayed kinetics of DNA double-strand break processing in normal and pathological aging. Aging Cell. 2008; 7:89-100.\*

Shao et al. Deficient of the DNA repair enzyme ATM in rheumatoid arthritis. Journal of Experimental Medicine. 2009; 60:1435-1449.\*

Kashishian et al, (2003), Molecular Cancer Therapeutics, 2 (12):1257-1264.\*

Shao; et al., "DNA-dependent protein kinase catalytic subunit mediates T-cell loss in rheumatoid arthritis", EMBO Molecular Medicine (2010), 2:415-427.

\* cited by examiner

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(57) **ABSTRACT**

Methods and compositions for improving immune system function are provided. These methods find particular use in improving immune system function in individuals with a condition in which naïve lymphocytes comprise elevated amounts of DNA double strand breaks (DSB), for example, individuals with Rheumatoid Arthritis, individuals that have received a bone marrow transplant, or elderly individuals, e.g. individuals that are 50 or more years old. Also provided are methods and compositions for screening for novel compounds that will improve immune system function in such individuals.

**14 Claims, 8 Drawing Sheets**